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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 28

Application Number: 08/726,211
Filing Date: October 4, 1996
Appellant(s): Tormo *et al.*

Jonathan D. Hurt
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed March 27, 2000.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 1-9, 31-37, 39-41, 48-50 and 52-54 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

The rejection of claims 1-8, 10-36, 39, 44, 48-50, 52-54 and 56 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

5,583034	Green *et al.*	12-1996
5,417,978	Tari *et al.*	5-1995

Reed WO 95/08350 March 30, 1995

Evan WO 93/20200 October 14, 1993

Abubakr *et al.* "Effectiveness of Bcl-2 antisense oligodeoxynucleotides (AS-ODN) against human follicular small-cleaved cell lymphoma (FSCCL)-SCID mice xenograft model." Blood vol. 84, no. 10 Suppl 1 (Dec. 1994) p. 374A.

Pocock *et al.* "In vivo suppression of B-cell lymphoma with Bcl-2 antisense oligonucleotides." Blood, vol. 82, no. 10 Suppl 1 (Dec. 1993), p. 200A.

Cotter *et al.* "Antisense oligonucleotides suppress B-cell lymphoma growth in a SCID-hu mouse model." Oncogene, vol. 9 (Oct. 1994) pp. 3049-3055.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-9, 31-37, 39-41, 48-50 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evan or Reed or Green *et al.* each in view of Tari *et al.*

Claims 1-8, 10-36, 44, 48-50, 52-54 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abubakr *et al.*, Pocock *et al.* and Cotter *et al.* together in view of Tari *et al.* and further in view of Evan.

(11) Response to Argument

Appellants' arguments for both grounds of rejection are based on the inappropriate use of Tari *et al.* in the rejections. Appellants argue (pages 7-9) that Tari *et al.* teaches the benefits of liposome compositions in general, not the use of neutral lipids rather than charged lipids. Appellants argue that the choice of phosphatidylcholine for the experiments was based on properties other than toxicity and that Tari *et al.* does not mention that the toxicity of neutral lipids is less that charged lipids, yet this is the premise upon which the rejection is based. Thus, the rejection is improper.

It is agreed that Tari *et al.* in the Summary of the Invention discusses the advantages of liposomes in general and states that phosphatidylcholines (which are uncharged lipids) and phosphatidylserines (which are charged lipids) are preferred embodiments. However, Tari *et al.* goes on to state that dioleoylphosphatidylcholine (DOPC), which is neutral, is a particularly preferred lipid (column 2, lines 10-14). Tari *et al.* states that phosphatidylcholines were used in the majority of disclosed experiments because phosphatidylcholine as a neutral molecule is compatible with methylphosphonate oligonucleotides and phosphatidylcholines are well-studied and easy to handle ((column 5, lines 18-22). Furthermore, all of the claims in Tari *et al.* are drawn to phosphatidylcholines and DOPC. DOPC is the only lipid actually

demonstrated to be effective for delivery of oliognucleotides to cells and shown to be non-toxic to cells (column 6, line 58-column 8, line 2). No claims are drawn to the disclosed embodiment of phosphatidylserines. Thus, a fair reading of the patent by one of ordinary skill in the art would lead the artisan to choose the neutral lipid phosphatidylcholine, likely DOPC, as the lipid of choice as Tari *et al.* uses only phosphatidylcholines in all but one of the working examples and specifically states why phosphatidylcholines were chosen over other lipids. The fact that Tari *et al.* did not base the choice of phosphatidylcholine on its lack of toxicity does not make the use of phosphatidylcholine any less obvious. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972); *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), *cert. denied*, 500 U.S. 904 (1991). Tari *et al.* points out the reasons for selecting phosphatidylcholines for use in liposomes containing oligonucleotides. This is sufficient motivation to one of ordinary skill in the art. Contrary to appellants' argument, the rejection is not based on the premise that neutral lipids are less toxic than charged lipids so this motivation does not need to be present in the references.

Appellants argue (pages 9-10) that the declaration of Drs. Tari and Lopez-Berestein clearly demonstrates the surprising and unexpected results that neutral lipids lack the toxicity of charged lipids. This evidence refutes the case for obviousness.

This argument is not deemed to be convincing. The results disclosed in the declaration are not commensurate in scope with appellants' alleged unexpected result that neutral lipids are less toxic than charged lipids. The experiments disclosed in the declaration used only one neutral lipid (DOPC) and two charged lipids (DMPG and DC-CHOL). Furthermore, the lipids were only tested at one ratio of neutral to charged lipids (70:30). Therefore, appellants do not have sufficient support to show that all neutral lipids are less toxic than all charged lipids. Additionally, Tari *et al.* discloses that liposomes composed of DOPC are not toxic to cells (column 1, lines 14-16). Thus, there is no surprise in the fact that DOPC is non-toxic.

Appellants argue (pages 10-11) that the rejection relies on the impermissible use of hindsight to argue that the claimed invention is not surprising. The Examiner must find the teaching or suggestion in the primary reference that uncharged liposomes are non-toxic relative to charged liposomes or liposomes in general.

This argument is not deemed to be persuasive. As stated above, the prior art does not need to show a motivation which is the same as appellants' motivation to make the claimed invention. Therefore, the prior art references do not need to teach or suggest that neutral lipids are less toxic than charge lipids or lipids in general. Tari *et al.* provides sufficient motivation to choose phosphatidylcholine in general or DOPC in particular. It is irrelevant that Tari *et al.* does not compare the toxicity of phosphatidylcholine to other lipids.

Appellants argue (pages 11-12) that since Tari *et al.* failed to explore the toxicity of charged liposomes it is deficient in establishing the generalized detriment of charged liposomes compared to neutral liposomes. Additionally, the prior art suggests the genus of liposomes while the present invention claims a species with a desirable yet unheralded property, so the invention cannot be said to be obvious.

This argument is not deemed to be persuasive. Tari *et al.* need not teach the detriment of charged lipids to neutral lipids in order to render the claimed invention obvious. It is only necessary that Tari *et al.* motivate one of ordinary skill in the art to choose a neutral lipid. As discussed above, Tari *et al.* clearly provides motivation to do so. The present invention does not claim a species of the genus disclosed by Tari *et al.* Rather, the present claims are drawn to a subgenus (neutral lipids) of the disclosed genus (lipids). However, appellants have not demonstrated a desirable yet unheralded property for all neutral lipids as they have only provided evidence regarding DOPC.

Appellants argue (page 13) that Tari *et al.* discloses that the desirable properties of lipids are common to all liposome constructs without a teaching, suggestion or guidance to use either charged or neutral lipids, let alone specifying the lipid DOPC. Thus, there is no proper motivation to specifically select neutral lipids as claimed.

This argument is not deemed to be convincing. Tari *et al.* clearly sets forth that DOPC is the preferred embodiment, uses only DOPC in the working examples, indicates that DOPC was chosen for certain advantageous characteristics and DOPC is the only specifically claimed lipid. This is undoubtedly a teaching, suggestion or guidance to use DOPC in a liposome/oligonucleotide composition. Since DOPC is an embodiment encompassed by the present claims the claimed invention is obvious.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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May 8, 2000

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